CURRENT DIGEST

of Scientific Papers Relating to Tobacco Use

(Compiled and Described for Informational Purposes Only for The Council for Tobacco Research—U.S.A. The Summaries Are Not Intended to be Complete Scientific Abstracts.)

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Attached to this issue of the Current Digest are excerpts from abstracts of papers presented at the following meetings:

1. AHA Council on Arteriosclerosis and American Society for the Study of Arteriosclerosis
2. American Heart Association Scientific Sessions

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1. SMOKING AND THE LUNGS

ASHLEY, David J. B., MD, MB, ChB, and DAVIES, H. Duncan, MB, MRCS, LRCP, Pathology Department, Morriston Hospital, Swansea, Wales

"Mixed glandular and squamous-cell carcinoma of the bronchus." (Thorax 22/5:431-436, September 1967)

"A group of 26 examples of lung carcinoma showing mixed squamous and glandular differentiation is described.... It is suggested that bronchial carcinoma is a single entity in which the type of cell, whether glandular or squamous, plays a much smaller part in determining the biological behavior than the anatomical site of the tumor and the degree of differentiation of its component cells....

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"This is shown to be a very specific reaction.... Considerable attention has been paid to the role of thiols as protective agents against mutagenesis by radiation and alkylating agents. The demonstration therefore of a mechanism by which tobacco smoke removes amino-thiols (especially cysteine)... would seem to be relevant to a possible hypothesis on the mechanism of carcinogenesis by tobacco smoke."

Cigarettes were smoked one at a time, for 6 minutes at an even rate, down to a 1/2 cm butt, the smoke passing directly into an aqueous solution of labeled cysteine, under conditions minimizing the amount of air drawn through the solution. The experiments were extended to main-stream smoke from pipe tobacco, and gave the same spectrum of products as obtained from cigarette smoke.

FERRI, Esther S., assistant director of Analytical Services, Northeastern Radiological Health Laboratory, U.S. Public Health Service, Winchester, Mass.; and CHRISTIANSEN, Howard, graduate student, department of epidemiology and public health, Yale University School of Medicine, New Haven, Conn.

"Lead-210 in tobacco and cigarette smoke." (Public Health Reports 82/9: 828-832, September 1967)

"Tests of six brands of cigarettes have shown that lead-210 is a component of mainstream smoke. These brands of cigarettes included two which were non-filtered, and one each with a cellulose filter, a cellulose and charcoal filter, a cellulose and charcoal filter with the tobacco treated for the removal of 'tars' and nicotine, and a cellulose filter with pipe tobacco.

"In smoke from five brands, the lead-210 activity was about half the polonium-210 activity. Compared with average levels of lead-210 inhaled from air in normal breathing, the intake of lead-210 from four brands of cigarettes was double the lead-210 in air, and in two brands was about equal to the lead-210 in air.

"A constant relationship between levels of radioactivity, tar, and nicotine content of the smoke could not be demonstrated. Using a recent model established by the International Commission on Radiological Protection, dosages to the pulmonary compartment of the respiratory tract were calculated, for each of the six brands, for a person smoking 20 cigarettes per day. These results showed that the radiation dose to the lung from inhalation of lead-210 in smoke plus the subsequent daughter ingrowth was equal to the dose from polonium-210 in smoke."

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"The close correspondence between the experimental and epidemiologic data makes it seem likely that the relation shown is one of general validity for populations having a dietary, beverage, and cigarette-smoking intake characteristic for American males..... The duration of time during which respiratory exposure occurs, as a fraction of the total week, does not appear to be as important as the total respiratory dose."

2. STATISTICAL

CHIAZZE, Leonard Jr., ScD, Director, Division of Biostatistics and Epidemiology, Georgetown University School of Medicine, and CIOCCO, Antonio, ScD, Chairman, Department of Biostatistics, University of Pittsburgh (Pa.) Graduate School of Public Health

"Intracommunity variation in cancer incidence for Pittsburgh." (Public Health Reports 82/9:759-770, September 1967)

"Results of a survey of the incidence of cancer in Pittsburgh, Pa. for the years 1957-58 were compared with results of a similar survey in 1947.... A substantial increase in the mortality from respiratory cancer in the United States has been noted for some time [NCI Monograph #6:133-350, 1961]. The evidence suggests that such an increase in risk is a true one although some part of the rise may not be real because of misclassification of tumors.

"Fifty-five per cent of all respiratory tumors among white residents of Pittsburgh enumerated in the 1947 survey were microscopically confirmed compared to 75 per cent in 1957-58. Although the proportion confirmed is higher in the later period, there is still room for error in assignments of cancer to the respiratory system. Nevertheless, the evidence seems to indicate that a real and substantial rise in the rate for respiratory cancer has taken place in Pittsburgh."

FISHBEIN, Morris, MD, Chicago, Ill., Editor

"Use and abuse of statistics." (Medical World News 8/41:120, October 13, 1967)

"The use and abuse of statistics, particularly in medical research, was recently discussed by Dr. Harry E. Ungerleider and Courtland C. Smith [CD, March 1967:10], leading authorities in the insurance field. In considering the current debate on cigarette smoking and lung cancer, they point out that the statistical relationship does not necessarily establish a cause-and-effect relationship...[and] believe that a specific causal connection between cigarette smoking and lung cancer is only a little better proved at this time than was the connection between unsanitary conditions and pellagra years ago.

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"Smoking histories were available in 19 men. One was a non-smoker, three smoked less than 10 cigarettes per day, nine smoked between 10 and 20 per day, three smoked between 20 and 30 per day, and three were simply recorded as cigarette smokers.... The mode of origin of these tumors is not difficult to understand.... When the bronchial epithelium is irritated it at first overacts, with the secretion of excessive mucus, but later undergoes metaplasia when the mode of differentiation of the cells is changed to that of a stratified squamous epithelium.

"This change, which is gradual rather than abrupt, is seen in the bronchial epithelium of cigarette smokers, who are accustomed to irritation of the mucosa (Auerbach, Stout, Hammond and Garfinkel, 1961), and involves permanent or semipermanent changes.... The morphology of neoplasms is not, of course, the only index of differentiation."

FISHMAN, Stanley I., MD, FACP, Chief, Pulmonary Function Unit, Jewish Hospital of Brooklyn, and Physician-in-Charge, City of New York Department of Health Chest Service, Williamsburgh-Greenpoint

"Pulmonary emphysema. Clinical problem." (New York State Journal of Medicine 67/19:2573-2585, October 1, 1967)

"The development of emphysema is a common late-occurring complication in a wide variety of chronic or recurrent lung diseases.... [A] degeneration of pulmonary elastic tissue has long been thought to be the primary initiating factor in emphysema.... More recently, the role of possible 'surfactants' acting at the fluid-tissue interface has stimulated considerable interest.... The foregoing is a brief attempt to indicate that the loss or diminution in elastic properties of the lung in emphysema may occur as a result of diseases not associated with previous obstructive disease....

"Regardless of how one feels about 'dry' emphysema, it is difficult to ignore the role of antecedent bronchitis entirely.... More to the point would seem a consideration of possible noxious agents and prevailing conditions which may cause either or both bronchitis and emphysema, and tobacco smoking holds the spotlight at present. This spotlight varies in brilliance according to one's point of view." The author then reviews papers by D. J. Baer (1966), O. Auerbach et al (1966), J. A. Hernandez et al (1966), and data of the National Tuberculosis Association and the 1964 Report of the Advisory Committee to the Surgeon General.

"The role of air pollution and inhalation of 'fumes' in producing or exaggerating chronic obstructive pulmonary disease is even more difficult to assess.... Well recognized, however, are the abrupt increases in the number of deaths of patients with chronic cardiopulmonary diseases which have occurred in communities during and after sudden, unusual increases in air pollution."

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"Oropharyngeal cancers form 39% of the total and show a geographical distribution which confirms the association with betel chewing, but does not support the thesis that tobacco leaf is the causative agent," the author says. "The striking sex disparities in the distribution of gastric cancers in different geographical areas make it unlikely that females enjoy any protection. These, on the other hand, make for environmental factors in the causation of... [gastric] cancer, which may be mainly in the pattern of diet and eating."

WENDEL, Horst, Medizinische Universitätsklinik, Rostock, East Germany

"Beziehungen zwischen Nikotinabusus and Lungenemphysem." (Zeitschrift für innere Medizin 21/24:777-780, December 1966: Author's English abstract)

The smoking habits of 1000 patients, one-half with emphysema, are compared, according to sex, age group, and rate of smoking. There were 65 male and 60 female non-smokers without emphysema and 30 and 59 respectively with emphysema; there were 98 male and no female heavy smokers (over 15 cigarettes, 10 pipes or 8 cigars daily) without emphysema, and 171 and 2 respectively with emphysema; there were more persons without emphysema than with the disease in the light and moderate smoking groups.

WYNDER, Ernest L., MD, and SHIGEMATSU, Takao, MD, Sloan-Kettering Institute for Cancer Research, New York City

"Environmental factors of cancer of the colon and rectum." (Cancer 20/9: 1520-1561, September 1967)

"The present study represents a retrospective investigation of 791 patients with cancer of the large bowel: 458 men and 333 women plus age-matched controls.... On the basis of the total epidemiologic evidence with which the data of the present study are consistent, dietary factors appear to be associated with the etiology of cancer of the large bowel. The dietary pattern that may fit the distribution of cancer of the large bowel includes a high intake of fats. The effect of this pattern appears to be more marked for cancer of the colon than cancer of the rectum....

"There is a slight association between cigar smoking and cancer of the large bowel in men. Cigar smoking is related to non-cigarette smoking particularly in men with cancer of the sigmoid colon. In turn, both of these factors relate to obesity and a Jewish affiliation. We regard cigar smoking and non-cigarette smoking as secondary and not primary associations."

3. TOBACCO CHEMISTRY

BRAVEN, J., BONKER, G. J., FENNER, M. L. and TONGE, B. L., College of Technology, and Freedom Fields Hospital, Plymouth; and College of Technology, Wolverhampton, England

"The mechanism of carcinogenesis by tobacco smoke. Some experimental observations and a hypothesis." (British Journal of Cancer 21/3:623-633, September 1967)

"This paper reports experimental evidence that when tobacco smoke is passed through an aqueous solution of cysteine at least 50% of the cysteine is converted into 2-methyl-L-thiazolidine-4-carboxylic acid by the acetaldehyde present in the smoke.

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Source: https://www.industrydocuments.ucsf.edu/docs/pnbl0000

PEACOCK, P. R. and SPENCE, J. B., Cancer Research Department, Royal Beatson Memorial Hospital, Glasgow, Scotland

"Incidence of lung tumors in LX mice exposed to (1) free radicals; (2) SO_2." (British Journal of Cancer 21/3:606-618, September 1967)

"Three comparable groups of LX mice of both sexes were examined for primary lung tumors and other lesions. Group 1, untreated controls [41 m, 39 f]; Group 2 exposed to inhalation of free radicals [30 m, 30 f]; and Group 3 exposed to inhalation of SO_2 [35 m, 30 f]....

"Free radicals were chosen partly because they are present in cigarette smoke, which is associated with cancer of the lung in man, and also because free radicals are generated in the electrostatic air filter which was used in previous experiments on the possible influence of airborne soot as a potential carcinogen for the mouse lung. Sulphur dioxide was chosen because of its presence in urban atmospheric pollution and because it is a gaseous and non-cumulative irritant which is easily controlled....

"No lung tumors were observed in mice below 300 days of age and only those which survived this age are considered in assessing the results."

Table IV. Actual number and (%) of LX mice over 300 days old with or without primary lung neoplasia or hyperplasia (Adapted by the Editor)

	No lung lesion	Primary carcinoma	Adenoma	Hyperplasia
Group 1: 35 males	24	2	11	3
30 females	23	-	5	3
Group 2: 29 males	16	3	12	4
30 females	22	-	7	3
Group 3: 28 males	13	2	15	5
30 females	16	4	13	3

SAINDELLE, Anatole, FLAVIAN, Nathalie, GUILLERM, Roger and HÉE, Jean, Laboratory of Physiology, New School of Medicine, Paris, France

"Libération d'histamine par la fumée de cigarette et ses constituants." (Comptes Rendus de l'Académie des Sciences de Paris, Series D, 264/25: 2926-2928, June 19, 1967: Translation)

Guinea pigs were subjected briefly to anesthesia, during which a high transection of the cervical spinal cord was performed, then were given artificial respiration, and insufflation pressure was recorded. After inhalation of two puffs of cigarette smoke, insufflation pressure increased in a few seconds, and returned to base value after about ten minutes. Arterial pressure, which reached very low values (30 mm Hg) following transection, remained unchanged after inhalation of cigarette smoke.

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Source: https://www.industrydocuments.ucsf.edu/docs/pnbl0000

HYAMS, Lyon, MD, SEGI, Mitsuo, MD (Japan), and ARCHER, Morton, MS, Environmental Health Foundation, New York City

"Myocardial infarction in the Japanese." (American Journal of Cardiology 20/4:549-554, October 1967)

"Seventy-nine Japanese men hospitalized with an electrocardiographically confirmed diagnosis of myocardial infarction and 157 age- and sex-matched controls were epidemiologically investigated. Serum cholesterol values were also obtained. The coronary group had significantly higher cholesterol concentrations. This was especially apparent in men under 50 years of age. In addition, these men smoked more cigarettes, and a greater proportion of them had a history of hypertension than others in the group. Obesity and stress did not differentiate the group....

"There was a statistically significant lower percentage of non-smokers in the study group than there was in the controls: 10.1 versus 21 per cent...." Smokers of 1 to 15 daily numbered 23 patients (32.4%) and 55 controls (44.4%); of 16-34 daily, 41 patients (57.7%) and 54 controls (43.5%); and of 35 or more cigarettes daily, 7 patients (9.9%) against 15 controls (12.1%). Also tabulated for both groups were number of years of smoking; and inhalation (or not) by ages under and over 50 years: 19 of 20 younger men with myocardial infarction said they inhaled.

JACKSON, Lt. David H., MC, USN, OBERMAN, Albert, MD, MITCHELL, Capt. Robert E., MC, USN, and GRAYBIEL, Ashton, MD, FACC, Naval Aerospace Medical Institute, Pensacola, Fla., the National Aeronautics Space Administration, and the U.S. Public Health Service

"Factors contributing to the ballistocardiographic waveform in healthy middle-aged men." (American Journal of Cardiology 20/4:531-540, October 1967)

Until studies of numerous factors affecting ballistocardiograms suggested in this paper have been conducted, "it seems that the knowledge that multiple factors appear to alter the ballistocardiographic acceleration waveform in varying degrees suggests caution in the quantitative use of the ballistocardiographic standards derived from groups in predicting stroke volume and other physiologic measures," the authors say.

Among various factors considered in the present preliminary study, cigarette-years of smoking contributed to several of the 15 multiple correlations considered, and were found to be a greater influence than the current amount of cigarette smoking. "Therefore, smoking may affect the cardiovascular functions in both acute and chronic fashion, as indicated by the ballistocardiogram."

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VERDY, Maurice, MD, FRCP(C), Hôpital Hôtel-Dieu, Montreal, Canada

"Effect of caffeine, nicotine and ethanol on lipolysis in human adipose tissue." (Revue Canadienne de Biologie 26/3:179-184, September 1967)

"The rate of lipolysis was studied in human adipose tissue in vitro by measuring the glycerol released in the incubation medium. Ethanol had no constant effect, even at doses of 4 mg/ml. Small doses of caffeine (10^{-4}M) failed to affect lipolysis or potentiate the lipolytic effect of adrenaline; but higher doses (10^{-3}M) did exert a lipolytic effect. Nicotine (10^{-4}M) had no direct effect, but reduced the lipolytic activity of adrenaline by 20%."

5. HEART AND CIRCULATION

CLARK, Virginia A., CHAPMAN, John M. and COULSON, Anne H., Division of Epidemiology, School of Public Health, and Department of Preventive Medicine, School of Medicine, University of California at Los Angeles

"Effects of various factors on systolic and diastolic blood pressure in the Los Angeles Heart Study." (Journal of Chronic Diseases 20/8:571-581, August 1967)

"The Los Angeles Heart Study, a prospective study of cardiovascular disease, began in 1950 with a physical examination of 1859 men [aged 21 years or more], sampled from persons working for civil service in Los Angeles.... There were 1315 subjects who had blood pressures taken in both 1950 and 1962.... Higher systolic blood pressures were found among similar age groups measured in 1962 compared to those found in 1950..... Covariance analyses indicated that higher blood pressures occurred among subjects who reported that they had not eaten for 2 hr or more or for 5 hr or more prior to examination as well as among non-smokers, alcohol users, and non-salt adders. The magnitude of the differences associated with these factors is probably not of clinical significance....

"The higher blood pressures occurred among the non-smokers, alcohol drinkers, and non-salt adders.... Among the subjects in this study, the cigarette smokers had an average Sheldon index [height/ $\sqrt[3]{\text{weight}}$] of 12.47 while the non-smokers were 12.34. Thus the smokers tended to be somewhat thinner... although the two means are less than a fourth of a deviation apart. Thus, the results of this study tend to confirm those of other studies in finding lower blood pressures, both systolic and diastolic, among cigarette smokers."

FRIEDMAN, Meyer, MD, and UHLEY, Herman N., MD, Mount Zion Hospital and Medical Center, San Francisco, California

"Management of coronary artery disease." (Postgraduate Medicine 42/3:155-162, September 1967)

"A behavior pattern (type A) characterized by an overwhelming sense of time urgency and competitive drive may be one of the most lethal of the suspected causes of coronary artery disease [CAD]....

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"Older physicians will remember that the cause of pellagra was at various times reported to be a contagious factor, a mold-contaminated maize, and unsanitary living conditions. On the basis of careful observation, Dr. Joseph Goldberger concluded that some dietary deficiency was the causative factor. He proceeded to test the effects of controlled diets in prisoners and hospital patients. His proof of a dietary deficiency led to the control of pellagra."

HAMMOND, E. Cuyler, ScD, JOHNSON, Herbert, BA, and PERCY, Constance, MS, Department of Epidemiology and Statistics, American Cancer Society, New York City

"Reporting of cancer of the lung, liver and uterus." (Cancer 20/10:1802-1806, October 1967)

"Copies of death certificates were obtained in a large epidemiologic study carried out in 25 states. When cancer was mentioned on a certificate, inquiry was made of the physician concerning primary site of cancer and basis of diagnosis. Information from the physician indicated that death certificate reporting of primary cancer of the lung is fairly reliable but that this disease may be somewhat under-reported as a cause of death...."

The data were derived from the ACS prospective study of more than 1,000,000 men and women, and are confined to cases where cancer was specified as the underlying cause of death either according to the death certificate or according to the physician's statement to the authors. After describing the pertinent international list rules for coding death certificates, the following tabulation of number of deaths from respiratory cancer was prepared:

Information from physician	No. of deaths by int'l. list coding of death certificates		
	Category 162	Category 163	Categories 165, 199, 227 or other tumor categories
Primary carcinoma of lung			
No uncertainty expressed	686	825	95
Some uncertainty expressed	13	31	11
Sarcoma of lung	3	3	0
Mesothelioma of pleura	0	10	4
Carcinoma of trachea	2	0	0
Subtotal	704	869	110
Cancer of other primary site	28	53	0
Cancer, primary site unknown	11	23	0
Grand total	743	945	110

#162 Malignant neoplasm of bronchus and of lung specified as primary
#162 Malignant neoplasm of lung unspecified as to whether primary or secondary
#165 Malignant neoplasm of thoracic organs specified as secondary
#199 Malignant neoplasm of unspecified primary site and other and unspecified primary sites
#227 Other benign neoplasm of muscular and connective tissue

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Source: https://www.industrydocuments.ucsf.edu/docs/pnbl0000

"Several experiments have shown that the particulate phase is very active, but to a lesser degree than the corresponding gaseous phase.... In addition, before causing total immobilization, it led to an intense cellular vibration, probably due to an abnormal augmentation of the frequency of movement of the cilia, the amplitude remaining constant; this phenomenon however never occurred with the gaseous phase, the algae turning over and over gently before ceasing movement. /Another test showed that/ nicotine plays little or no part in the activity of the particulate phase...."

Elution of several fractions of the particulate phase, tested in turn on the algae, led to subfractioning and chromatographic analysis of the more active components, and hydroquinone was identified at a significant concentration of about 70 micrograms per cigarette or more. Synthetic hydroquinone was then tested on the algae. It was further confirmed that phenol caused the phenomenon of vibration before immobilizing the algae.

"From the above, we can deduce that the hydroquinone of the particulate phase, like the acrolein of the gaseous phase, can inhibit the movements of the cilia of the algae and it is not impossible that it would be the same for the ciliated epithelium of the respiratory tract of men. Moreover, one cannot exclude the possibility of a more profound biological action, either directly or after transformation into benzoquinone. In fact we have found spectrophotometrically that this transformation occurs very rapidly in the presence of human saliva, at a dilution of 1 in 4, and it could be that even the tobacco smoke itself may contain benzoquinone. This compound, of which the irritant properties and the reactivity with thio-compounds are known, could in our opinion play a part in the genesis of certain pathological processes."

PALECEK, F. and AVIADO, D. M., University of Pennsylvania School of Medicine, Philadelphia

"Prisoevek k mechanismu ucinku cigaretoveho koure na bronchialni sval." (Contribution on the mechanism of the effect of cigarette smoke on the bronchial muscle). (Authors' abstract: 19th Physiological Days, Prague, January 27, 1967: Ceskoslovenska Fysiologie 16/3:266, 1967: Translation)

When cigarette smoke is inhaled, pulmonary resistance increases and pulmonary flexibility decreases. The following observations testify to the participation of histamine in that response: a) Pulmonary resistance and flexibility were measured in dogs narcotized by Mead and Whittenberger's method. Inhalation of cigarette smoke and histamine aerosol and intravenous injection of nicotine caused increase of pulmonary resistance which was blocked by atropine. Those three stimulations cause bronchoconstriction by partial stimulation of the vagus. b) Blocking histamine synthesis by administering alpha-hydrazin-histidine leads to suppression of the bronchoconstrictive response to the inhalation of cigarette smoke. c) In narcotized cats the responses to cigarette smoke, nicotine and histamine aerosol were of the same type as in dogs but somewhat less expressed. Premedication with alpha-hydrazin-histidine led to suppression of response not only to cigarette smoke but also to intravenous nicotine and histamine. d) Narcotized rabbits did not react to any of the stimulations. No pulmonary mechanism sensitive to histamine, nicotine or cigarette smoke is found in the rabbit.

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Source: https://www.industrydocuments.ucsf.edu/docs/pnbl0000

"A great deal of attention recently has been directed toward the possible noxiousness of cigarette smoking in patients with CAD. The close statistical association of heavy cigarette smoking and increased clinical incidence of CAD is irrefutable. But the meaning of such association remains unclear, particularly when heavy pipe and cigar smokers appear to suffer no more from CAD than non-smokers. We are quite uncertain whether heavy cigarette smoking itself aggravates the course of CAD or whether the behavior pattern (type A) of those who smoke excessively is the real culprit. At this juncture, however, we still would advise discontinuance of cigarette smoking....

"All these general measures (diet control, cholesterol-lowering drugs, avoidance of cigarettes, physical exercise) are essentially useless in forestalling the course of CAD if the behavior pattern (type A) of the patient is not altered."

HERXHEIMER, A., MB, Senior Lecturer in Pharmacology, and GRIFFITHS, R. L., HAMILTON, A. and WAKEFIELD, Marion, medical students, London Hospital Medical College, England

"Circulatory effects of nicotine aerosol inhalations and cigarette smoking in man." (Lancet 2:654-755, October 7, 1967)

The authors compared the circulatory effects of smoking a standard filter-tip cigarette and a filter-tip cigarette made from cured lettuce leaves (without nicotine) with the effects of an aerosol containing nicotine and of a control aerosol without nicotine in five healthy volunteers (one a women) aged 20 or 21 years. All had smoked 5 to 15 cigarettes daily, with inhalation, for three years.

"Inhalation of cigarette smoke and nicotine aerosol significantly increased pulse rate and blood pressure during the period of inhalation, and these two treatments produced similar increases; the control smoke and the control aerosol had no effect.... There was little difference between the basal values on different occasions in the same volunteer. The effects became apparent 1 or 2 minutes after the subject started to inhale nicotine, and then remained fairly constant. However, the peak effect on pulse rate and blood pressure tended to occur later during cigarette smoking than with nicotine aerosol inhalations....

"Since the circulatory effects of inhaling nicotine aerosol so closely match those of cigarette smoking, the use of nicotine aerosol as a substitute deserves investigation. It might be particularly useful in patients with respiratory disease who have difficulty in giving up cigarettes."

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MASUDA, Yoshito, MORI, Kazuko and KURATSUNE, Masanori, Faculty of Medicine, Kyushu University, Fukuoka, Japan

"Studies on bladder carcinogens in the human environment. I. Naphthylamines produced by pyrolysis of amino acids." (International Journal of Cancer 2/5:489-493, September 15, 1967)

"It appears that the present investigation is the first to demonstrate the formation of 1- and 2-naphthylamines during pyrolysis of amino acids. The aromatic amines seem to be formed by radical reactions between low molecular compounds produced during pyrolysis. The data suggest that naphthylamines may be formed from other compounds containing nitrogen by incomplete combustion at temperatures around and above 700°C.

"It is conceivable that naphthylamines are formed in the process of tobacco smoking since about 5% of tobacco consists of nitrogen compounds such as proteins and alkaloids, and since the combustion of tobacco during smoking occurs at temperatures above 700°C even during puff intermission (Wynder and Hoffmann, 1964). Further experiments are needed to substantiate the hypothesis of naphthylamine formation during tobacco smoking."

4. BIOLOGICAL EXPERIMENTS

DALHAMN, T., HOLMA, B. and TOMENIUS, L., National Institute of Public Health, Karolinska Institutet, Stockholm, Sweden

"In vitro studies of the ciliotoxic action of ethanol vapor in relation to its concentration in tracheal tissue."* (Acta Pharmacologica et Toxicologica 25/2:272-280, 1967)

"The ciliostatic action of respiratory irritant gases and vapors has frequently been investigated.... The available literature contains no reports on the tissue concentrations of ciliotoxic gases at the time of ciliostasis.... The purpose of this paper was to observe the association between the concentration of ethanol vapor and the duration of exposure preceding ciliostasis in rabbit trachea in vitro, and also to determine the concentration of ethanol in tracheal tissue at the time of ciliostasis.... In this investigation the tissue concentration of ethanol required to arrest tracheal ciliary activity in vitro was about 4%, irrespective of the size and age of the specimen, the atmospheric concentration of ethanol vapor and the duration of exposure preceding ciliostasis...."

*(Ed.note: The authors acknowledge the support of the U.S. National Institutes of Health and the AMA-ERF Committee for Research on Tobacco and Health in conducting this work.)

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Source: https://www.industrydocuments.ucsf.edu/docs/pnbl0000

LEHMAN, Edward W., PhD, SCHULMAN, Jay, PhD, and HINKLE, Lawrence E. Jr.,
Division of Human Ecology, departments of medicine and psychiatry,
Cornell University Medical College, New York City

"Coronary deaths and organizational mobility. The 30-year experience of 1160 men." (Archives of Environmental Health 15/4:455-461, October 1967)

"Each of the 65 men who died of coronary heart disease was matched with another man of similar age and education who had died of another cause at about the same time, and with a survivor of similar education and age, whose career was studied up to the time at which his paired companions had died..... /The mobility-immobility data suggest/ that intraorganizational mobility not only has several dimensions but also has numerous correlates. It is possible that the effects of many of these factors on coronary heart disease may be at cross-purposes and that they may actually 'mask' the influence of certain mobility experiences.

"For example, data still under analysis suggest that even when education is held constant, 'more mobile' men are less prone to exhibit such potentially important 'risk' factors as obesity and heavy smoking. Hence, if the experience of upward mobility is positively linked to coronary heart disease, this relationship may be obscured by other factors that are not experiential.... Mobility per se appears to be a more psychologically salient factor for the 'college' than for the 'non-college' men."

McCANN, Mary B., MD, and STARE, Fredrick J., MD, FAPHA, Harvard University
School of Public Health, Boston, Mass.

"The contribution of animal studies to nutritional discoveries that have benefited both animals and man." (American Journal of Public Health 57/9: 1597-1604, September 1967)

"Over the past five years we have studied Irish-born Bostonians and their brothers living in Ireland. The men in Ireland eat almost 800 calories more each day, than their brothers in Boston, yet they are leaner by 8 per cent. The brothers in Ireland exercise more. They also consume more eggs and butter. A higher percentage of their fat is from animal sources (90 per cent in Ireland versus 84 per cent in Boston) and their diet contains more cholesterol, 911 mg versus 824 mg.

"Both levels are higher than most American men consume. Yet the serum cholesterol level of the brother in Ireland is slightly, but not significantly, lower than that of the brother in Boston. It certainly is not higher, and pathological studies of autopsy specimens show less extensive vascular disease in Ireland. This project has taught us the therapeutic value of physical exercise."

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"The authors discuss possible mutual relations of peptic ulceration and cancer of the lungs." Five men and 1 woman did not smoke; five men and 1 woman smoked 10-20 cigarettes daily, three men 25-30 daily, and one man 60 daily; one man smoked an unknown amount.

FIGUEROA RAMIREZ, David, MD, NADAL, Hector M., MD, FACS, and ESCANAVERINO, Raul Betran, MD, FACS, Veterans Administration Hospital, San Juan, and University of Puerto Rico School of Medicine

"Carcinoma of the oral cavity and pharynx." (Boletin de la Asociacion Medica de Puerto Rico 59/4:188-195, April 1967)

"From 1951 to 1965 one hundred forty cases of carcinoma of the oral cavity and pharynx were admitted to this hospital. Of these, one hundred twenty-five patients with carcinoma of the tongue, floor of the mouth, tonsils, and hypopharynx were selected for this study.... Fifty-six patients were alcoholics, eighty-two were heavy smokers, and fifty-two /of the foregoing/ indulged in both habits."

GAVEY, C. J., MD, MB, FRCP, MRCS, LRCP, Institute of Ophthalmology, University of London, England

"A physician's assessment of 300 patients in a glaucoma clinic." (British Journal of Ophthalmology 50:689-700, December 1966)

"Glaucoma is an acute or chronic condition characterized by, but not invariably associated with, raised ocular tension.... Of the 300 patients, roughly two-thirds were male and one-third female.... Just over one-fifth of all patients did not smoke, and just under two-thirds did not smoke significantly.... The proportion of heavy smokers was small (9.66 per cent).... One-quarter of all patients took no alcohol and over four-fifths took only small amounts, while only 2.66 per cent drank heavily....

"Glaucoma, like many other diseases of special senses, appears at times to be a purely local disturbance, yet a study of the patient as a whole as in the present work does suggest that systemic disease has in fact a considerable influence in determining the onset, source, and severity of glaucoma, and it behooves us in treatment to give deliberate attention to such general factors. For example, a glaucomatous chronic bronchitic who smokes may benefit from cessation of smoking, by diminishing cough, improving respiratory function, and reducing vascular tone and ischemia."

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GOLDSMITH, John R., MD, Chief, Environment Hazards Evaluation Unit, California State Department of Public Health, Berkeley

"Suspected link between air pollution and rising lung cancer unsupported by studies." (California's Health 25/3:10-11, September 1967)

The California Health "Department's present view is that exposure to air pollution in California is not an adequate explanation for the increase in lung cancer; however, observation and study of this problem must be continued. Cigarette smoking is viewed as the major causal factor in lung cancer."

GOLDSMITH, John R.

"Environmental epidemiology and the metamorphosis of the human habitat." (American Journal of Public Health 57/9:1532-1547, September 1967)

"Carbon monoxide is one of the most thoroughly studied of industrial contaminants and a great deal is known about its toxicity and the mechanisms affecting high-level exposure. Less is known about its effects at low levels over long periods of time.... Studies of atmospheric carbon monoxide and carboxyhemoglobin in traffic policemen have been carried out in Paris by Moureu and his associates.... [Apparently a personal communication; much of the data cited not found in H. Moureu et al, Proc. Roy. Soc. Med. 57:1015, 1964]

"When the data are separated for traffic policemen according to whether the policemen are smokers or not, the results [Fig. 3&4: not found in Moureu] suggest that the cigarette smokers who started work with relatively high carboxyhemoglobin levels, and who cannot smoke during work, tended to excrete carbon monoxide and at the end of their period of duty had lower carboxyhemoglobin. The smokers who started duty with low levels tended to have an increase. Those who started with levels of about 5 per cent blood carboxyhemoglobin showed very little change. However, in the study confined to non-smokers (Figure 4) it is seen that these exposures in heavy traffic to increase the carboxyhemoglobin by measurable levels....

"Possibly some of the health effects from cigarette smoking are also related to carbon monoxide exposure. Psychomotor effects from low-level short-term exposures should be studied, as well as effects of long-term exposures on red blood count and hemoglobin metabolism from long-term exposure."

GOLDSMITH, J. R. and HEXTER, Alfred C.

"Respiratory exposure to lead: Epidemiological and experimental dose-response relationships." (Science 158:132-134, October 6, 1967)

"In recent epidemiologic studies, cigarette smokers have been shown to have slightly but consistently higher values of blood lead than non-cigarette smokers [CD, December 1961:10]. This can be traced to lead and arsenic in leaf tobacco grown in soils on which arsenate sprays were formerly used. Cigarette smoke is also known to retard ciliary clearance of particles impacted in the tracheobronchial tree, which could tend to increase absorption of inhaled lead....

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Altogether, 1688 were coded by death certificates to categories 162 and 163, while according to what the physicians said, 1573 (93.2%) of these were primary cancers, the authors say. In addition, 110 deaths due to primary cancer of the lung and pleura were not coded to categories 162 and 163.

"Not infrequently the physician who signs a death certificate does not have the full record of the case readily at hand when he does so," they say. "Thus, if we had written to physicians for further information on all deaths, it is virtually certain that we would have found that an appreciable number of deaths attributed (on death certificates) to causes other than cancer were actually due to primary cancer of the lung. We conclude that the number of deaths coded to categories 162 and 163 is an underestimate of the number of deaths due to primary cancer of lung according to the best available medical information."

KRISHNA, Gopal, SAXENA, O. N. and SINGH, A. K., G.S.V.M. Medical College, Kampur, India

"Oral carcinoma." (Indian Journal of Surgery 29/5:229-235, May 1967)

"The present study comprises 776 cases of oral carcinoma treated... from 1st January to 31st October, 1964..... 600 (77.33%) were Hindus and 176 (22.67%) Muslims..... Out of 400 cases of carcinoma of the buccal mucous membrane, 368 patients chewed tobacco and 288 lime and nuts, 224 had been smokers, and 360 had oral sepsis [more than one factor being present in many cases]. Corresponding figures for carcinoma of tongue (192 cases) were 144 (tobacco chewing), 80 (lime and nuts), 96 (smoking) and 176 (oral sepsis). [The gingiva were third with]... tobacco chewing (48 cases), lime and nuts (24 cases) and oral sepsis (48 cases). Smoking accounted for 40 out of 56 cases of carcinoma of the lips."

MALHOTRA, S. L., Medical Department, Western Railway, Bombay, India

"Geographical distribution of gastrointestinal cancers in India with special reference to causation." (Gut 8/4:361-372, 1967)

The study concerns a population of 1,034,000 railway employees aged 18 to 55 years and 1,017,000 adult dependents (wives and widowed mothers); the clinical data are derived from 86 hospitals maintained by eight Indian railways and extra facilities provided for the treatment of cancer. Of 470 proved alimentary system cancers seen in 1960 to 1964 inclusive, 183 related to the buccal cavity (143 m, 40 f), 53 to the esophagus (46 m, 7 f) 83 to the stomach (73 m, 10 f), 59 to the intestines and rectum (42 m, 17 f), 26 to the liver (16 m, 10 f), and the remainder to other and unclassified areas.

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MULCAHY, Risteard, MD, MRCP, HICKEY, Noel, MB, MRCPI, and MAURER, Brian, MB, BCh, St. Vincent's Hospital, and University College, Dublin, Eire

"Coronary heart disease in women. Study of risk factors in 100 patients less than 60 years of age." (Circulation 36/4:577-586, October 1967)

"Three dominant factors were hypertension, cigarette smoking, and hypercholesterolemia. Cigarette smoking and hypertension were present together or separately in 80 to 90% of the patients.... It is believed that the proper control of hypertension in the population and the elimination of cigarette smoking would cause an appreciable or even dramatic reduction in the incidence of precocious and middle-aged coronary heart disease in women."

There were 63 smokers, 33 non-smokers, and 4 ex-smokers in the group, compared to 45.6%, 45.3% and 9.1% respectively in the female population of Eire aged 35 to 59 years, as reported by Research Services Ltd. in April 1962.

6. OTHER SYSTEMIC CONDITIONS

BARLOW, David H., and BAER, Daniel J., Boston College, Mass.

"Effect of cigarette smoking on the critical flicker frequency of heavy and light smokers." (Perceptual and Motor Skills 24/1:151-155, February 1967)

The authors tested 60 male college students aged 18 to 21 years, all of whom had been habitual smokers for at least one year, inhaled, and reported no visual defects; 30 smokers of 20 to 40 cigarettes daily were classified as heavy smokers, and 30 smokers of 5 to 15 daily as light smokers. One-half of each group smoked one cigarette during the experiment and one-half did not smoke at that time. All observed a cigarette, food and beverage deprivation for at least one hour prior to testing and avoided strenuous activity for at least 12 hours before testing.

Although both groups of smokers showed a significant elevation in critical flicker frequency (CFF) immediately after smoking, the CFF of light smokers gradually returned to pre-smoking levels (in about 15 minutes), while the CFF of heavy smokers first rose significantly, fell below pre-smoking levels (in about 10 minutes), and then rose again above pre-smoking levels. "The biphasic effect for the heavy smokers may have been undetected in previous investigations for several reasons," the authors say. "Not only did these require much longer smoking deprivations than the 1-hr period of the present study, but all smokers, regardless of amount habitually smoked, were treated as one group."

DRAZILOVA, V. and NINGEROVA, A., III Vnitrini Klinika Lekarske Fakulty Brno, Czechoslovakia

"Vredova nemoc a rakovina plic." (Peptic ulceration and lung cancer). (Casopis Lekaru Ceskych 106/7:181-184, February 19, 1967: Authors' English Summary)

The authors examined 100 patients (98 men and 2 women) with bronchial cancer. "In 17 instances a combination with gastroduodenal ulcer was revealed, whereby the ulcer usually preceded cancer....

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Source: https://www.industrydocuments.ucsf.edu/docs/pnbl0000

DAVIS, Thomas R. A., MD, DTMH, MPH, BATTISTA, S. P., MS, and KENSLER, C. J., PhD, Arthur D. Little, Inc., Cambridge, Mass.

"Mechanism of respiratory effects during exposure of guinea pigs to irritants."* (Archives of Environmental Health 15/4:412-419, October 1967)

"Respiratory function of intact and tracheotomized guinea pigs was studied in response to inhalation of a variety of substances...." including 40 ml puffs of smoke from unfiltered cigarettes. In each experiment, a control period of 10 minutes preceded an exposure period of 8 minutes. Respiratory measurements were made at 10 and 30 seconds after the initiation of each of eight puffs. Following exposure, each animal was observed for an additional eight minutes.

"In the intact animal, an increased resistance ($P < 0.01$) was observed ten seconds after the puff along with a decreased respiration rate ($P < 0.01$) and a decreased minute volume ($P < 0.01$). In each case, there was rapid recovery between each exposure. Tidal volume remained unchanged while compliance was slightly decreased ($P < 0.05$). In tracheotomized animals exposed to puffed cigarette smoke, changes from control values for resistance, tidal volume, and minute volume were not statistically significant. On the other hand, respiration rate was significantly ($P < 0.01$) increased while compliance was... slightly decreased ($P < 0.05$)....

"On the basis of data presented, it is concluded that receptors exist in the nasopharynx and larynx of the guinea pig which can be stimulated by both irritant vapors and substances which are normally considered chemically inert (polystyrene particles and saline mist). Although other receptors probably exist, those required to produce the observed effects are not present in the trachea or the lung."

*(Ed.note: The authors acknowledge the support of Liggett and Myers Tobacco Co. in conducting this work.)

EPSTEIN, Samuel S., ANDREA, J., JAFFE, H., JOSHI, S., FALK, H. and MANTEL, N., Childrens Cancer Research Foundation, Inc., and Harvard Medical School, Boston, Mass.; and National Cancer Institute, Bethesda, Md.

"Carcinogenicity of the herbicide maleic hydrazide." (Nature 215:1388-1390, September 23, 1967)

"We report here a high incidence of remote tumors, hepatomas, after subcutaneous injections of maleic hydrazide in infant mice.... While human populations in general are continuously exposed to maleic hydrazide, it is difficult to compute the level of this exposure. It can be assumed that each day an adult male ingests approximately 1.5 mg of maleic hydrazide from potatoes and onions and inhales 0.27 mg from forty cigarettes, assuming residues of 10 ppm in potatoes and onions and 132 ppm in tobacco of which 6.7 per cent is found in smoke.

"A resulting annual exposure to about 630 mg of maleic hydrazide is some twelve times greater than doses found here to be very carcinogenic.... It would thus seem appropriate to reduce tolerance levels of maleic hydrazide or ban its use, except when human exposure can be minimized."

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Source: https://www.industrydocuments.ucsf.edu/docs/pnbl0000

GIAMMONA, Samuel T., MD, Department of Pediatrics, University of Miami (Fla.) School of Medicine

"Effects of cigarette smoke and plant smoke on pulmonary surfactant." (American Review of Respiratory Disease 96/3:539-541, September 1967)

"Five dogs, 5 cats, and 20 guinea pigs were exposed in vivo in separate cages in a specially constructed plastic chamber to an individual aerosol of cigarette smoke. The dogs and cats were exposed three hours daily for one week, and the guinea pigs were exposed three hours daily for three weeks.... At the end of the period the animals were sacrificed by intravenous injections of pentobarbital.... There was no significant change in surface tension observed in lung extracts from the dogs and cats.... The lung extracts from the guinea pigs, however, demonstrated a significant change in the maximal surface tension.

"Ten guinea pigs were also exposed to the gas phase, and there was no change in either the minimal or maximal surface tension of the extracted surfactant.

"After in vitro exposure of pulmonary surfactant [from normal dogs] to cigarette smoke, both dry and in saline solution, there was a significant decrease in the maximal surface tension.... There was no significant change noted in the minimal surface tension. Five mg of the dry pulmonary surfactant was exposed to the gas phase only, and no significant differences were observed in the maximal and minimal surface tension....

"Smoke produced from lettuce leaf smoking product and from pine and avocado leaves caused similar changes in the surface tension measurements of pulmonary surfactant in vitro. This consisted of a significant increase in the minimal surface tension and a significant decrease in the maximal surface tension after these plant smoke exposures. There was a significant decrease in the surfactant activity index after plant leaf smoke exposure....

"These observations suggest that plant smoke exposure would favor the development of atelectasis, whereas tobacco smoke exposure would initiate changes in surfactant favoring the development of emphysema."

IZARD, Camille, MORÉE-TESTA, Paulette, and LACHARPAGNE, Jacqueline, Research and Equipment Directorate, SEITA, Paris, France

"Effets des condensats de fumée de cigarette sur la motilité de Dunaliella bioculata Butcher." (Comptes Rendus de l'Académie des Sciences de Paris, Series D, 264/20:2379-2381, May 17, 1967: Translation)

"In a previous note [CD, June 1967: 16] we have reported the inhibitory effect of the gaseous phase of cigarette smoke on the motility of Dunaliella bioculata Butcher: we have also demonstrated the important part played by acrolein in this effect. Subsequently, using the same technique, we have undertaken an investigation of the particulate or condensate phase and the preliminary results obtained are reported below....

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"We established that the total increase in the insufflation pressure observed after inhalation of cigarette smoke is really due to a decrease in pulmonary compliance and to an increase in dynamic expiratory resistance....

"We also studied the effect of cigarette smoke in animals with intact spinal cords. In this case, inhalation of two puffs of cigarette smoke did not increase the insufflation pressure consistently. When it did increase, it generally returned to its initial value in one minute. In addition, a very large increase was observed in the arterial pressure....

"We investigated what constituents of cigarette smoke might be responsible for this bronchoconstricting action. First we found that the gaseous phase of the smoke is involved as much as the particulate phase. The severity of the bronchospasm is reduced but not entirely eliminated by putting in a filter which removes the particles. The bronchospasm does not seem to be related to the nicotine present in cigarette smoke; and it was also seen after inhalation of smoke from cigarettes made of corn silk.... It seems to be caused by the presence of short-chain aldehydes, such as acetaldehyde and acrolein, in the smoke.

"We administered a mixture containing only these two compounds to guinea pigs in which the spinal cord had been transected... [and] found that the inhalation of two puffs [of the mixture] caused a bronchospasm with an intensity and course comparable to those obtained after inhalation of the same volume of filtered cigarette smoke. The effects of cigarette smoke and its aldehyde constituents on the ventilatory mechanics in the guinea pig are analogous to those of histamine. That is why we investigated whether cigarette smoke and its constituents are capable of liberating histamine from the tissues. For this study we used in vivo experiments and experiments in isolated organs.

"In vivo in the rat we studied the effect of one of the most active constituents of cigarette smoke, acetaldehyde, on mesentary mast cells. It is well known that most of the endogenous histamine is found stored in these cells. After intraperitioneal injection of acetaldehyde, the mast cells underwent pronounced cytological changes analogous to those observed during anaphylactic shock. At the same time, some histamine appeared in the peritoneal fluid.

"In vitro we showed that the water-soluble phase of the cigarette smoke is capable of liberating histamine from isolated guinea pig lung kept at 37°C in a maintenance fluid. The quantity of histamine liberated is very much higher than that liberated in anaphylaxis.... On the other hand, nicotine was shown to have no effect at all. Thus, it seems that acetaldehyde is basically responsible for the liberation of histamine caused by cigarette smoke.... [Further experiments showed that] the mechanism involved in liberation of histamine by acetaldehyde appears to be different from that which occurs in anaphylactic shock."

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Source: https://www.industrydocuments.ucsf.edu/docs/pnbl0000